CHAPTER

43 LAXATIVES AND CATHARTICS

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Laxatives and cathartics are drugs that promote defecation. Valid indications for the use of these agents are limited. The contrasting extensive misuse of self-prescribed cathartic nostrums by the public is a result of the many misconceptions concerning bowel function and of the mistaken notions of the value of cathartic medication. Persistence of this misuse reflects the failure of the medical and ancillary health professions to counter the proprietary drug advertising designed to perpetuate these erroneous beliefs.

The terms *laxative* and *cathartic* correctly imply different intensities of drug effect. Laxative effect suggests the elimination of a soft, formed stool, whereas cathartic effect implies a more fluid evacuation. When applied to the *effect* of a drug, this distinction is convenient and should be preserved. Most drugs that promote defecation produce a laxative effect in low dosage but a cathartic effect in higher dosage. Consequently, when applied to the *drugs* themselves, the terms are often employed interchangeably.

The numerous laxative-cathartic preparations available for "over-the-counter" use have been reviewed by the United States Food and Drug Administration Advisory Review Panel (FDA, 1975).

GENERAL CONSIDERATIONS

Laxatives and cathartics constitute a varied group of drugs. The major common characteristics are oral efficacy and activity that is primarily due to their physical properties within the intestinal lumen or to contact with the intestinal mucosa. Interestingly, the effects of several of the laxative-cathartics are due to products of biotransformation of the drug by the intestinal microflora.

Mechanisms of Laxative-Cathartic Effects. Laxatives and cathartics increase the water content of the feces and speed transit of the intestinal contents by one or more of three general mechanisms: (1) Water and electrolytes may be retained in the intestinal lumen by the *hydrophilic* or *osmotic* properties of the drug or its metabolites, with intestinal transit being increased indirectly due to increased intestinal bulk. (2) The laxative-cathartic may act on the mucosa to decrease normal *net absorption of electrolytes and water,* with intestinal transit being increased indirectly by the fluid bulk. (3) The laxative-cathartic may increase transit by primary effects on *intestinal motility,* with net absorption of electrolytes and water being decreased indirectly because of the reduced time for absorption.

Views about the mechanism of action of the individual laxative-cathartics are changing (*see* FDA, 1975; Gaginella and Phillips, 1975; Binder, 1977; Fingl and Freston, 1979). Traditional explanations have been reexamined, and most have been modified, if not discarded. Unfortunately, the mechanism of action of all laxative-cathartics remains uncertain. For example, it is now recognized that a primary effect of many cathartics is inhibition of the net absorption of electrolytes and water by the intestine. Yet, at least some of these agents also influence intestinal motility directly, and the relative contributions of the two types of actions to the laxative-cathartic effect *in vivo* remain to be determined. Moreover, analysis of the biochemical mechanisms that underlie laxative-cathartic effects is still rudimentary. The possible role of the gastrointestinal hormones, prostaglandins, and cyclic nucleotides as mediators of laxative-cathartic effects is just beginning to be explored in a systematic manner. However, as this analysis proceeds, the laxative-cathartic agents can be expected to be useful tools for defining the role of these mediators in intestinal physiology and pathology and for clarifying the interrelationship between intestinal transport of electrolytes and water and intestinal motility. The mechanisms of laxative-cathartic effects

are considered further in subsequent discussions of the individual agents.

The term *stimulant cathartic*, previously employed to refer to drugs that increase intestinal motility, should be abandoned. These drugs are now known also to have primary effects on the absorption of electrolytes and water, and the effects on motility are a combination of excitatory and inhibitory actions. A suitable substitute term is *contact cathartic*. It is appropriately noncommittal with regard to the relative contributions of the various actions to the laxative-cathartic effects *in vivo*, and it correctly implies that these drugs act on the intestine, as contrasted with those that act primarily by their hydrophilic or osmotic properties.

Classification and Choice of Laxatives and Cathartics. The laxatives and cathartics are classified and discussed in the text to emphasize mechanism of action. However, the more commonly used agents are listed in Table 43-1 without regard to mechanism of action in order to identify the major groups of drugs and to indicate the pattern of laxative-cathartic effects produced in *usual clinical dosage*. It must be emphasized, however, that the effect and latency of all laxatives and cathartics vary with dosage. The major groups of drugs (*e.g.*, bulk-forming agents, docusates) often have distinguishing pharmacological characteristics that influence their choice for a specific patient. Nevertheless, agents within a group usually have similar clinical usefulness and limitations.

DIETARY FIBER AND RELATED BULK-FORMING LAXATIVES

A fiber-rich diet, in conjunction with other nonpharmacological measures, is the most appropriate method for prevention and treatment of functional constipation. Dietary fiber is also of benefit for patients in whom it is desired that the feces be maintained soft, to avoid straining at the stool, and in the management of irritable bowel disease and diverticular disease of the colon. The related bulk-forming agents are natural and semisynthetic polysaccharides and cellulose derivatives similar to those characterized as dietary fiber. They are useful as a supplement to dietary adjustment or when a constipating, fiber-poor diet cannot be corrected.

The term *dietary fiber* has supplanted the older term *crude fiber*. Dietary fiber is defined physiologically as the portion of plant food that escapes digestion in the human small intestine. Chemically, it consists of cellulose and lignin, the components measured by the method for crude fiber, and also gums, pectins, hemicelluloses, and other polysaccharides. The polysaccharide components are now considered to be more important. The content of total dietary fiber of many foods is three to four times that of the crude fiber.

Because of differences in their component polysaccharides, dietary fiber from various sources and the related bulk-forming agents vary somewhat in their pharmacological characteristics. Unfortunately, these differences are as yet poorly defined, and choice among these preparations often depends upon preference of the individual patient. An excellent review of dietary fiber has been provided by Cummings (1973); the properties of the bulk-forming laxatives have been summarized by Tainter and Buchanan in a symposium (1954).

Table 43-1. CLASSIFICATION AND COMPARISON OF REPRESENTATIVE LAXATIVES AND CATHARTICS

LAXATIVE-CATHARTIC EFFECT AND LATENCY IN USUAL CLINICAL DOSAGE *		
Softening of Feces, 1 to 3 Days	*Soft or Semifluid Stool, 6 to 8 Hours*	*Watery Evacuation, 1 to 3 Hours*
Bulk-forming laxatives Bran Psyllium preparations Methylcellulose	Diphenylmethane cathartics Phenolphthalein Bisacodyl	Saline cathartics † Sodium phosphates Magnesium sulfate Milk of magnesia
Docusates (dioctyl sulfosuccinates)	Anthraquinone cathartics Senna Cascara sagrada Danthron	Castor oil
Lactulose		
Mineral oil		

* Effect and latency of all laxatives and cathartics vary with dosage.
† Also employed in lower dosage for laxative effect.

Effects on the Intestinal Tract. Dietary fiber and related agents increase the mass of stool, its water content, and the rate of colonic transit. These effects are usually apparent within 24 hours, but full effect during repeated use may be delayed for several days or longer. Alterations of the metabolism of bile acids and cholesterol, gas production, and other effects are variable. The laxative effect is commonly attributed to the hydrophilic bulk-forming properties of the component polysaccharides. However, a likely additional factor is metabolism of the polysaccharides by the intestinal microflora, with accumulation of metabolites that are osmotically active. Active metabolites may also alter intestinal transport of electrolytes and/or motility and cause subtle changes in fecal bile acids and fecal flora.

Bran and other bulk-forming agents reduce intraluminal rectosigmoid pressure and relieve symptoms in patients with irritable bowel disease and diverticular disease of the colon. Relief of pain and other symptoms occurs progressively over several months (*see* Parks, 1974; Brodribb, 1977). However, a causal role for lack of dietary fiber in disorders of the large bowel and other diseases remains to be established (*see* Goldstein, 1972; Cummings, 1973; Painter and Burkitt, 1975; Mendeloff, 1977).

Because of their ability to absorb water and to provide an emollient intestinal mass, the bulk-forming laxatives have some usefulness for the symptomatic relief of *acute diarrhea* and to modify the effluent in patients with an *ileostomy* or *colostomy*. However, loss of sodium, potassium, and water may be increased in such patients. The alleged effectiveness of the bulk-forming agents as appetite suppressants in the management of *obesity* has *not* been established.

Adverse Effects. The bulk-forming laxatives have minimal systemic effects. However, possible alterations of glucose tolerance and calcium metabolism are still incompletely defined. Allergic reactions have been reported for several of the natural products.

Flatulence may occur, particularly if the dosage of dietary fiber or bulk-forming agent is increased abruptly; it can sometimes be relieved by adjusting the dosage, switching to a different preparation or different source of fiber, or increasing the fluid intake. The bulk-forming agents potentially adsorb other drugs administered concurrently, thereby interfering with their intestinal absorption, but solid evidence is lacking.

Intestinal obstruction has been reported after administration of the bulk-forming agents, and *impaction* may result when there is gross intestinal pathology. These agents should not be employed in individuals with intestinal ulceration, stenosis, or adhesions. Occasional cases of *esophageal obstruction* have also occurred when these agents have been swallowed dry or when the tablets were chewed. *Patients who have difficulty swallowing should be warned not to take these preparations dry, and generous amounts of water should be prescribed with all bulk-forming laxatives.*

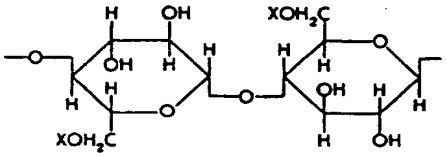
Bran and Other Dietary Fiber. Bran, a by-product of the milling of wheat, contains more than 40% dietary fiber and is the most convenient source of intestinal bulk. Crude bran is rather unpalatable, but the processed form makes a pleasant cereal or may be taken in the form of cookies and muffins. Bran-rich cereals contain 25% dietary fiber.

A helpful guide to the fiber content of foods has been provided by Burkitt and Meisner (1979). For prevention of constipation, they recommend substitution of wholemeal bread for white bread and sufficient bran or breakfast cereal to provide 6 to 10 g of dietary fiber daily.

Psyllium (Plantago) Preparations. *Plantago Seed*, U.S.P., is obtained from various species of plantain. The seeds contain a large amount of natural mucilage and form a gelatinous mass on contact with water. However, the whole seeds have now been largely replaced by powdered preparations of the mucilaginous component. Typical preparations are *plantago ovata coating* (KONSYL) and *psyllium hydrophilic mucilloid* (METAMUCIL, L.A. FORMULA). The latter preparation also contains dextrose as a dispersing agent and provides 14 kcal per 7-g dose. The usual dose of these preparations is 4 to 10 g, one to three times daily, stirred in a glassful of water or other liquid.

Chronic administration of the psyllium preparations may produce modest reduction of plasma cholesterol concentration, apparently by interference with reabsorption of bile acids. Sensitization, with asthmatic symptoms upon inhalation of psyllium powder, has been reported in atopic individuals chronically exposed to the powder during its manufacture.

Methylcellulose and Carboxymethylcellulose Sodium. *Methylcellulose*, U.S.P., and *Carboxymethylcellulose Sodium*, U.S.P., are hydrophilic semisynthetic cellulose derivatives. They are marketed under many trade names. Methylcellulose has the following structure:



Methylcellulose

Methylcellulose and carboxymethylcellulose sodium have similar laxative properties. Methylcellulose is available as official tablets (500 mg) and oral solution (450 mg/5 ml) and also as a syrup (985 mg/5 ml) and powder; carboxymethylcellulose sodium is available largely in combination with other laxatives and as a powder. The usual adult dose is 1 to 6 g daily, in divided dosage. During chronic medication, smaller doses may be satisfactory. The dosage for children is 500 mg, two or three times daily. Both preparations should be taken with ample water.

Other Bulk-Forming Agents. Other hydrophilic substances that differ little from those described include *Polycarbophil,* U.S.P., and *powdered karaya (sterculia) gum. Allergic reactions,* characterized by urticaria, rhinitis, dermatitis, and asthma, have been attributed to the latter preparation. Daily adult dosage for these preparations is 4 to 6 g and 5 to 10 g, respectively.

SALINE CATHARTICS

The saline cathartics include various magnesium salts and several sulfates and phosphates. These salts are often employed in full dosage when prompt, thorough evacuation of the bowel is desired, as prior to certain diagnostic procedures. They are also used in lower dosage for a laxative effect, but frequent administration should be avoided. Since they have many common characteristics, the saline cathartics are conveniently considered as a group. The distinctive features of the individual drugs are mainly palatability, cost, and risk of untoward systemic effects.

Laxative-Cathartic Effects. Full doses of the saline cathartics (15 g of magnesium sulfate or its equivalent) produce a semifluid or watery evacuation in 3 hours or less. Low doses produce a laxative effect with greater latency. The saline cathartics are incompletely absorbed from the digestive tract and retain water in the intestinal lumen by their osmotic properties. Intestinal transit is increased indirectly. However, since magnesium salts cause the secretion of cholecystokinin from the duodenal mucosa, Harvey and Read (1975) have suggested that cholecystokinin-mediated pancreatic secretion and increased secretion and motility of the small intestine and colon may contribute to the cathartic effect.

Systemic Effects. Some absorption of the component ions of the saline cathartics does occur, and in certain instances they may produce systemic toxicity. In an individual with impaired renal function, the accumulation of magnesium ions in the body fluids may be sufficient to cause intoxication (*see* Chapter 35). Magnesium cathartics should thus be administered only if renal function is adequate. Similarly, sodium salts may be contraindicated in patients with congestive heart failure, and phosphate salts may reduce the concentration of ionized calcium in plasma.

The luminal contents of the intestinal tract remain essentially isosmotic. Consequently, hypertonic solutions of the saline cathartics can produce significant dehydration. For this reason, the saline salts should be administered with sufficient water by mouth to ensure that no net loss of body water occurs.

Magnesium Salts. *Magnesium Sulfate,* U.S.P. (*Epsom salt*), is one of the traditional saline cathartics. The official dose is 15 g, but 5 g (about 40 mEq of magnesium ion) or less produces a significant laxative effect when the salt is administered in dilute solution to a fasting individual. The intensely bitter taste may be partially masked by taking the salt in lemon juice.

Milk of Magnesia, U.S.P., is a 7.0 to 8.5% aqueous suspension of magnesium hydroxide. The usual adult dose is 15 to 30 ml (about 40 to 80 mEq of magnesium ion); the dose for children is 0.5 ml/kg. *Magnesium Hydroxide,* U.S.P., is also available as tablets. The usual dose is 2 to 4 g (80 to 160 mEq). Other magnesium salts commonly employed as gastric antacids have similar laxative properties (*see also* Chapter 42).

Magnesium Citrate Oral Solution, U.S.P., is a pleasant-tasting, but expensive, saline cathartic. It is a flavored, effervescent solution that provides the equivalent of 3 to 4 g of magnesium hydroxide in the official 200-ml dose.

Sodium Phosphates. Phosphate salts are relatively pleasant-tasting saline cathartics. The most frequently employed preparation is *Sodium Phosphates Oral Solution,* U.S.P. Each 10 ml contains 1.8 g of sodium phosphate and 4.8 g of sodium biphosphate. The official dose is 10 to 20 ml, taken diluted and with ample additional water. *Sodium Phosphates Enema,* U.S.P., is employed for rectal administration. The official 120-ml dose contains 7.2 g and 19.2 g of the two salts, respectively. Sodium phosphate is also available as citrate-flavored sodium phosphate solution. The usual 10-ml dose provides 7.5 g of sodium phosphate.

Other Saline Cathartics. *Sodium Sulfate,* U.S.P. (*Glauber's salt*), is one of the cheapest saline cathartics, but it is the most objectionable as far as taste is concerned. The usual dose is 15 g. *Potassium Sodium Tartrate,* U.S.P. (*Rochelle salt*), *Effervescent Sodium Phosphate,* U.S.P., and other saline cathartics that contain tartrates are pleasant-tasting agents. However, there is insufficient evidence to establish safe and effective dosage for the tartrates (FDA, 1975).

A large number of proprietary saline cathartic preparations are available. They range from expensive natural mineral waters, for which extravagant claims are made, to salts that differ little from those described above.

CONTACT CATHARTICS

The contact cathartics are agents that act on the intestinal mucosa and have effects both on the net absorption of electrolytes and water and on motility. Included in this group are the *diphenylmethane* derivatives, the *anthraquinones, castor oil,* the *docusates* (dioctyl sulfosuccinates), and the *bile acids.* Despite similarity of their mechanism of action, the clinical uses and limitations of these agents are sufficiently varied to require separate description. These differences de-